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# The doping level of boron-doped diamond electrodes affects the voltammetric sensing of uric acid

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In this work, the electrochemical oxidation and subsequent determination of uric acid was investigated using boron-doped diamond electrodes with various B/C ratios (0–2000 ppm). The cyclic voltammetric study showed one irreversible oxidation peak at + (1.1–1.25) V (vs. Ag/AgCl/3 M KCl) in the presence of Britton–Robinson buffer (pH 2.25) depending on the boron content. Employing differential pulse voltammetry using the 2000 ppm boron-doped diamond electrode the acquired analytical parameters were as follows: a limit of detection of 7.7  $\mu\text{M}$ , a limit of quantification of 26  $\mu\text{M}$  and intra-day repeatability (relative standard deviation of 2.9% for  $n = 15$ ). After performing an interference study, the method was applied to the determination of uric acid in biological samples (human urine). The uric acid concentrations determined in the urine samples were compared with the reference values stated in the literature. The proposed methodology using boron-doped diamond electrodes could find applications in uric acid sensing within clinical, pharmaceutical and environmental analysis.

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## 1. Introduction

Uric acid (UA) (IUPAC name: 7,9-dihydro-1H-purine-2,6,8(3H)-trione) is a metabolic product of purine present in blood and urine. Abnormal UA levels are linked to several diseases such as hyperuricemia, gout and chronic renal diseases.<sup>1</sup> Altered levels of UA in human serum might be used as a measurable indicator. Excessive levels could be caused by leukemia or cardiovascular diseases, and lower UA levels might be related to multiple sclerosis.<sup>2</sup> Hence, the development of novel methods for reliable quantification of UA in biological fluids is significant of the diseases treatment.

Up to now, various analytical methods and procedures for the determination of UA have been developed including high performance liquid chromatography,<sup>3</sup> capillary electrophoresis,<sup>4</sup> chemiluminescence,<sup>5</sup> colorimetry,<sup>6</sup> amperometric detection<sup>7</sup> and biosensing.<sup>2,8</sup> In general, chromatographic methods are time-consuming with high implementation costs, oftentimes with the need for preconcentration and derivatization

steps. Therefore, sensitive, simple, fast, efficient and non-toxic methods for the quantification of UA in biological fluids and environmental samples are still needed.

In the past few years, electrochemical methods based on chemically modified electrodes have been extensively used for the determination of UA. Various nanomaterials (multi-walled carbon nanotubes<sup>9</sup> and carbon nanospheres<sup>10</sup>) and nanoparticles (graphene<sup>11</sup> and gold<sup>12</sup>) were used due to their excellent physical and chemical properties, activity and large active surface area to modify carbonaceous electrodes. So far, nanocomposites<sup>13</sup> and nanoparticles in polymeric matrices<sup>14</sup> have also been largely used for UA sensing. However, it should be taken into account that chemical modifications are usually time-consuming and more expensive with complicated modification protocols, oftentimes involving the synthesis of polymeric matrices.

Since its introduction, boron-doped diamond (BDD) is extensively used for electroanalytical purposes.<sup>15</sup> Because of the advantageous features (wide potential range, weak adsorption, low background currents, chemical stability, and biocompatibility) and commercial availability<sup>16</sup> of this electrode material, it has been used as an alternative to common carbonaceous and chemically modified electrodes. Over the last decade a lot of effort has been made to determine various biologically active compounds in the clinical,<sup>17</sup> food<sup>18</sup> and environmental<sup>19,20</sup> fields using BDD electrodes.

In regard to UA, Yu *et al.* investigated the influence of BDD electrodes prepared by hot filament chemical vapor deposition with different boron levels (3500–7500 ppm) on its detection.

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Electrodes were characterized by Raman spectrometry and SEM. Differential pulse voltammetry proved that BDD with higher boron concentration presented higher sensitivity to UA, a lower limit of detection (LOD) and a wider linear concentration range (LCR). A LCR from 0.09 to 250  $\mu\text{M}$  and a LOD of 2.1  $\mu\text{M}$  were obtained for the 7500 ppm electrode. Differential pulse voltammetry proved that increasing the B/C ratio provided higher stability to UA, a lower LOD and a wider LCR, which could be attributed to a stronger current response.<sup>21</sup>

In this manuscript, the electrochemical oxidation and subsequent determination of UA was investigated using bare BDD electrodes. For this purpose, a set of BDD electrodes with B/C ratios between 0 and 2000 ppm were used and the analytical parameters and sensitivity of each electrode were evaluated using both DPV and SWV. In the interference study, the influence of common urine compounds was tested. The developed method was subsequently applied to the quantification of UA in biological fluids (urine). The determined UA concentration levels in urine were compared to reference values stated in the literature.

## 2. Experimental

### 2.1 Chemicals

All chemicals (Sigma Aldrich, Slovakia) used in this work were of analytical grade. BR buffer was prepared by mixing phosphoric acid, acetic acid and boric acid, all components at 0.04 M concentration and adjusted with 0.2 M sodium hydroxide to the required pH. The stock standard solution of UA (0.01 M) was prepared in a small aliquot of a water–sodium hydroxide mixture (1 : 10, v/v) and subsequently filled up to the line. Working solutions of lower UA concentrations were freshly prepared on the day of experiments. Solutions were prepared with water with a resistivity of not less than 18.2 M $\Omega$  cm at 25 °C. Stock solutions were stored in a refrigerator at 6 °C. All experiments were carried out at ambient temperature.

### 2.2 Apparatus

A PSTAT mini potentiostat (Herisau, Switzerland) was used and controlled by using PSTAT electrochemical software. A standard three-electrochemical configuration was used, employing an argentochloride reference electrode, a platinum microdisc electrode (diameter of 2 mm) as a counter electrode and BDDE with a B/C ratio of 0, 1000 and 2000 ppm and a diameter of 740  $\mu\text{m}$  each as a working electrode. The fabrication of such hot filament chemical vapour deposition (HF-CVD) BDD electrodes was described previously.<sup>22,23</sup> The pH of solutions was measured using a pHenomenal® pH 1100L meter (VWR, Slovakia).

### 2.3 Measurement procedures

The electrochemical behavior study of UA and its determination were carried out using cyclic voltammetry (CV), differential pulse voltammetry (DPV) and square wave voltammetry (SWV). After optimizing the experimental parameters, a calibration curve was obtained by successive addition of aliquots of the UA standard solution (0.01 M) into the electrochemical cell already

containing the supporting electrolyte; each concentration was measured in triplicate. The linear least-squares regression in OriginPro 8.0 (OriginLab Corporation, USA) was used for data evaluation. The limit of detection (LOD) and limit of quantification (LOQ) were calculated as three and ten times the standard deviation of the current response for the blank solution divided by the slope of the calibration curve.

### 2.4 Sample preparation

Human urine samples (U1–U3) were taken from healthy volunteers immediately before experiments. At the time of experiments and shortly before, the volunteers did not undergo any treatments with multivitamin formulations and other drug dosages. These experiments were performed in compliance with a named law (Parliamentary Act no. 40/1964 Coll. Civil Code as amended). Informed consent was obtained from the volunteers prior to the experiments. An aliquot volume of particular fresh urine (0.5 mL) was placed into the electrochemical cell already containing 24.5 mL supporting electrolyte. Subsequently, aliquots (0.3, 0.6 and 0.9 mL) of UA stock solution were added and the analysis was conducted using the standard addition method ( $n = 3$ ).

## 3. Results and discussion

### 3.1 Electrochemical behaviour of UA on BDD electrodes

For this study, the set of BDD electrodes with various B/C ratios of 0, 1000 and 2000 ppm was chosen. The conductivity of these electrodes is supposed to be below the metallic threshold with the boron concentration below the level of  $10^{20} \text{ cm}^{-3}$ .<sup>24</sup> The electrochemical oxidation of UA was progressively studied by cyclic voltammetry (CV) in the presence of Britton–Robinson buffer solution (BR buffer) in the pH range of 2.25–12. For each working electrode, a decrease of peak current ( $I_p$ ) was observed with increasing pH. For this reason, the best results were obtained in acidic media (results not shown). Next, the measurements on each BDD electrode in BR buffer (pH 2.25) were accomplished presenting one irreversible anodic peak. As can be seen, with increasing B/C ratio (0–2000 ppm) there was a slight shift towards negative potentials with the peak potential ( $E_p$ ) starting from +1.3 to +1.1 V (Fig. 1). This finding suggests that the kinetics of the electrode reaction of UA on these electrodes are different and the oxidation of UA proceeds most readily on the 2000 ppm BDD electrode with the highest magnitude of UA peak current. The background current for all of the electrodes was sufficiently low (e.g. in the range of 0.1–0.2  $\mu\text{A}$  at the potential of +2.0 V), thus confirming one of the benefits of using BDD electrodes.

The scan rate study was carried out by cyclic voltammetric measurements of 0.5 mM UA in BR buffer pH 2.25 on the 2000 ppm BDD electrode at scan rates in the range of 10–200  $\text{mV s}^{-1}$ . The influence of scan rate on the oxidation peak of UA is shown in Fig. 2. With increasing scan rate values, the anodic peak shifts slightly to positive potential values. This feature is typical for irreversible electrochemical reactions. The peak currents showed a linear relationship with the square root

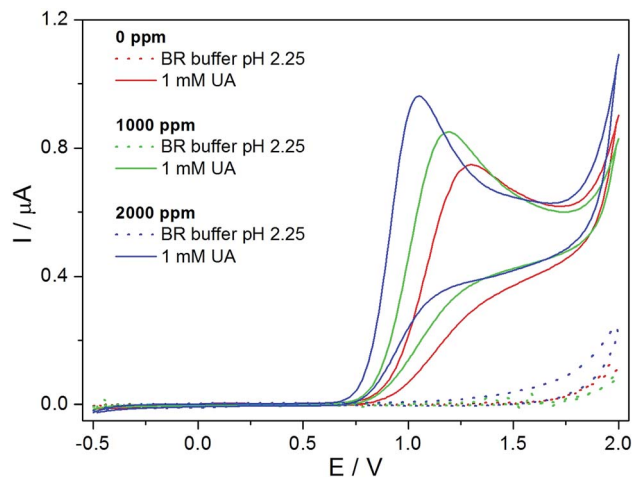


Fig. 1 CV records of blank (BR buffer pH 2.25) and 1 mM UA in BR buffer pH 2.25 using 0–2000 ppm BDD electrodes, scan rate  $100 \text{ mV s}^{-1}$ .

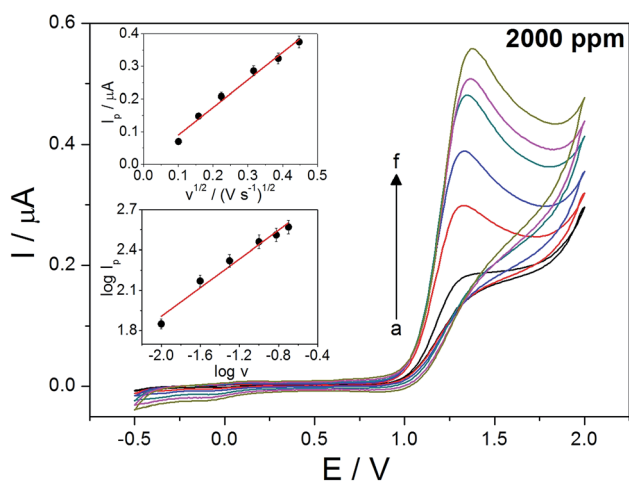


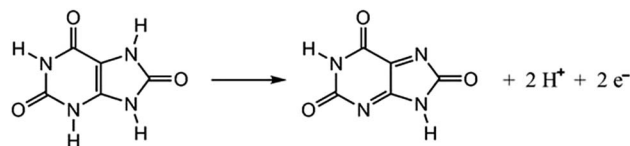
Fig. 2 CV records of 0.5 mM UA in BR buffer pH 2.25 using the 2000 ppm BDDE; scan rates: (a) 0.01, (b) 0.025, (c) 0.05, (d) 0.1, (e) 0.15, and (f)  $0.2 \text{ V s}^{-1}$ . The dependencies  $I_p = f(v^{1/2})$  and  $\log I_p = f(\log v)$  are appended in the inset.

of the scan rate ( $R^2 = 0.981$ ) suggesting that the reaction is under diffusion control. Similar behavior was observed in the case of 0 and 1000 ppm electrodes. This phenomenon could also be confirmed by plotting  $\log I_p = f(\log v)$  with a slope of 0.534 ( $R^2 = 0.968$ ) which is in good line with the theoretical value (0.5) typical for diffusion controlled reactions.<sup>25</sup>

### 3.2 Electrode reaction mechanism study

The number of electrons taking part in the electrochemical oxidation of UA was estimated using the Laviron equation (eqn (1)):

$$E_p = \frac{RT}{\alpha nF} \ln v \quad (1)$$



Scheme 1 Electrochemical oxidation of UA.

where  $R$  is the gas constant ( $8.314 \text{ J K}^{-1} \text{ mol}^{-1}$ ),  $T$  is the temperature (298 K),  $F$  is the Faraday constant ( $96\,500 \text{ C mol}^{-1}$ ) and  $\alpha$  is the transfer coefficient (for an irreversible system, it was taken as 0.5). By plotting  $E_p$  vs.  $\ln v$  (the graph is not shown), the number of electrons was estimated to be  $n = 2.14$ , which is in good agreement with the theoretical value stated in the literature.<sup>12</sup> In general, the mechanism of UA electrochemical oxidation is believed to occur *via* two electron and two proton transfer to form an imine of UA (Scheme 1).

### 3.3 Calibration curves and analytical performance

In order to obtain the well-defined peaks with the highest magnitude and best peak shapes for further quantitative analysis, differential pulse voltammetric (DPV) and square wave voltammetric (SWV) parameters were necessary to be optimized. For DPV, a modulation amplitude of 100 mV and a modulation time of 100 ms were determined for all working electrodes. In the case of SWV, a frequency of 10 Hz and an amplitude of 50, 50 and 100 ms were obtained for the BDD electrodes with a B/C of 0, 1000 and 2000 ppm, respectively.

The quantification of UA was studied under optimized experimental conditions on the set of BDD electrodes with different B/C ratios. With increasing UA concentration, the current response was recorded employing DPV (Fig. 3) and SWV (Fig. 4). The respective calibration curves were plotted and are shown in the insets of Fig. 3 and 4. The analytical parameters obtained by DPV and SWV are summarized in Tables 1 and 2.

Based on the data, the best sensitivity was obtained in the case of the BDD electrode with a 2000 ppm B/C ratio (0.68 and  $1.2 \text{ mA M}^{-1}$  for DPV and SWV, respectively). Importantly, in the case of SWV, the sensitivity of the 2000 ppm electrode was 6.3 times higher when compared to the 0 ppm electrode and 2.7 times higher when compared to the 1000 ppm electrode. As

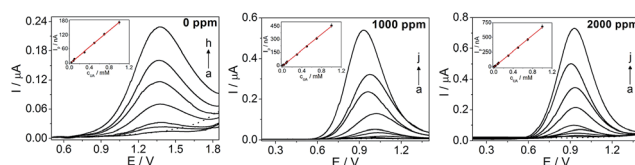


Fig. 3 DP voltammograms of various concentrations of UA applying optimal experimental parameters in BR buffer pH 2.25 using 0–2000 ppm BDD electrodes: 0 ppm: (a) 0, (b) 0.04, (c) 0.08, (d) 0.1, (e) 0.3, (f) 0.5, (g) 0.7, and (h) 1 mM; 1000 ppm: (a) 0, (b) 0.008, (c) 0.02, (d) 0.04, (e) 0.08, (f) 0.1, (g) 0.3, (h) 0.5, (i) 0.7, and (j) 1 mM; 2000 ppm: (a) 0, (b) 0.008, (c) 0.02, (d) 0.04, (e) 0.08, (f) 0.1, (g) 0.3, (h) 0.5, (i) 0.7, and (j) 1 mM. Peak current as a function of UA concentration appears in the inset.

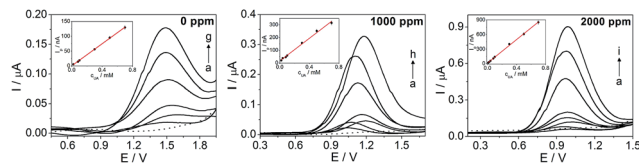


Fig. 4 SW voltammograms of various concentrations of UA applying optimal experimental parameters in BR buffer pH 2.25 using 0–2000 ppm BDD electrodes: 0 ppm: (a) 0, (b) 0.02, (c) 0.08, (d) 0.1, (e) 0.3, (f) 0.5, and (g) 0.7 mM; 1000 ppm: (a) 0, (b) 0.02, (c) 0.04, (d) 0.08, (e) 0.1, (f) 0.3, (g) 0.5, and (h) 0.7 mM; 2000 ppm: (a) 0, (b) 0.008, (c) 0.02, (d) 0.04, (e) 0.08, (f) 0.1, (g) 0.3, (h) 0.5, and (i) 0.7 mM. Peak current as a function of UA concentration appears in the inset.

Table 1 Analytical parameters for the determination of UA on various BDD electrodes using DPV

B/C (ppm)	Intercept (nA)	Slope (mA M <sup>-1</sup> )	SD of the intercept (nA)	SD of the slope (μA M <sup>-1</sup> )	R <sup>2</sup>	LOD (μM)
0	−3.9	0.18	1.4	2.8	0.999	24
1000	−5.3	0.46	1.1	5.0	0.999	8.5
2000	−5.2	0.68	1.7	7.1	0.999	7.7

Table 2 Analytical parameters for the determination of UA on various BDD electrodes using SWV

B/C (ppm)	Intercept (nA)	Slope (mA M <sup>-1</sup> )	SD of the intercept (nA)	SD of the slope (μA M <sup>-1</sup> )	R <sup>2</sup>	LOD (μM)
0	0.61	0.19	0.84	2.2	0.999	14
1000	16	0.44	2.2	15	0.993	15
2000	14	1.2	3.1	19	0.998	7.7

a result of a low LOD (7.7 μM), wide linear concentration range (0.008–1 mM) and well-defined peaks, the 2000 ppm electrode was chosen for further measurements. This finding is in good line with the results of Yu *et al.*,<sup>21</sup> where increasing the B/C ratio (3500–7500 ppm) presented a lower LOD, wider LCR and stronger current response. However, it should be taken into account that they used the BDD working electrodes with considerably higher boron doping levels (metal conductivity). On the basis of the proposed work, the electrochemical behavior of UA on BDD electrodes with various B/C ratios (semiconductor conductivity) is a complex issue with a relationship between the B/C ratio and the current response. The electrochemical properties of such electrodes are in general strongly influenced by non-uniform doping in diamond, boundary effects, varied ratios of graphite to diamond (sp<sup>3</sup>/sp<sup>2</sup>), surface morphology and termination.<sup>26,27</sup>

According to the literature survey,<sup>9–14,21,28–38</sup> the utilization of a GCE and CPE as a working electrode is dominant in the electrochemical determination of UA. Until now, the methodology using a pencil graphite electrode (PGE) modified with over-oxidized poly(3,4-ethylenedioxythiophene) nanofibers has been considered to be the most sensitive with the lowest

LOD of 0.001 μM.<sup>28</sup> In comparison, the LOD of the herein proposed method (7.7 μM) is higher; however, it is sufficient for the determination of UA in human urine (the concentration of UA in urine ranges from 1.4 to 4.4 mM).<sup>7</sup> Moreover, it was obtained without any chemical modification of the working electrode. In this sense, chemical modification of the electrode might be considered as a time-consuming and tedious procedure. A detailed comparison of so far published methodologies for the quantification of UA is shown in Table 3.

The precision of the proposed method was evaluated using the 2000 ppm electrode by DPV and SWV measurements (*n* = 15) at the UA concentration level of 0.5 mM over the short interval time (intra-day repeatability). The RSD was found to be 2.9% and 6.9% for DPV and SWV, respectively, confirming negligible adsorption of the UA and its oxidative products onto the BDD electrode surface. Because of a lower RSD value, DPV was chosen as a sensitive voltammetric technique for the quantification of UA in the human urine samples.

### 3.4 Interference study

The selectivity of the proposed method was tested by DPV using the 2000 ppm BDD electrode. The concentration level of UA was set to 1 mM with the addition of a particular interferent in the following concentration ratios: 1 : 0.3, 1 : 0.6, 1 : 1. Common compounds that can be found in biological fluids as well as environmental samples such as caffeine, glucose, ascorbic acid and dopamine were chosen for this study (Fig. 5). The results indicated that a significant influence of dopamine was recorded at the concentration ratio of 1 : 1. Peak potentials corresponding to particular compounds (0.88 V and 0.77 V *vs.* Ag/AgCl for UA and dopamine, respectively) were too close, thus causing possible interference. The oxidation signal of UA slightly decreased with increasing caffeine concentration. Glucose did not influence the peak magnitude of UA. In the case of ascorbic acid, a significant influence was observed at the concentration ratio of 1 : 1. At this level, the magnitude of the UA oxidation peak doubled, confirming that ascorbic acid underwent oxidation at the same potential under specified experimental conditions.

To sum up, the utilization of the proposed method can be limited by the presence of the above-mentioned compounds (depending on the concentration ratio) thus lowering the selectivity.

### 3.5 Determination of UA in urine

The developed method was applied to the determination of UA in human urine samples (U1–U3). The volunteers did not undergo any treatment with multivitamin formulations and other dosages, and thus the presence of higher concentrations of ascorbic acid in urine was not expected. The analysis was performed by DPV using the 2000 ppm BDD electrode under optimized experimental conditions. The preparation of the sample is described in the Experimental section. Quantification of UA was carried out by means of the standard addition (SA) method with respective volumes of 0.3, 0.6 and 0.9 mL 0.01 M



Table 3 Comparison of various electrochemical platforms for the quantification of UA<sup>a</sup>

Electrode	Modifier	Electrolyte	LCR ( $\mu\text{M}$ )	LOD ( $\mu\text{M}$ )	Sample	Reference
CPE	AuNPs	PBS pH 6.0	1.2–21	0.12	Urine	12
CPE	FCNs	PBS pH 7.0	0.5–9	0.04	Blood	10
GCE	3DGH-Fc	PBS pH 7.0	8–400	0.06	Serum	13
GCE	Au/ZnO/PP/rGO	PBS pH 7.0	1–680	0.09	Urine	29
GCE	GO-MnNH <sub>2</sub> TPP	PBS pH 7.0	20–290	1.74	Urine	30
GCE	NiCu/C	PBS pH 7.0	0.5–110	0.05	Urine	31
GCE	Poly(CTAB)	PBS pH 7.0	1–1000	0.33	Urine	32
GCE	Co-CeO <sub>2</sub>	PBS pH 5.0	1–2200	0.43	Urine	33
GCE	PAA-nano-Au	PBS pH 6.5	5–1000	0.3	Calf serum	34
GCPE	B-CeO <sub>2</sub>	PBS pH 5.0	0.42–12	0.005	Serum and urine	35
GCPE	In-CeO <sub>2</sub>	PBS pH 5.0	0.08–15	0.007	Serum and urine	36
GNS	Au/PDDA	PBS pH 7.0	6–156	2.0	Urine	14
GPE	POMANS-MWCNT	PBS pH 6.0	0.6–52	0.15	Urine and serum	9
IDA	Au/NPs-GO/Au	PBS pH 7.0	2–1050	0.62	Urine	37
ITO	GF	PBS pH 7.4	0.02–60	0.003	Injection and urine	11
PGE	Ox-PEDOT-nf	PBS pH 2.0	0.01–20	0.001	Serum and urine	28
SPE	$\beta$ -CD/rGO	PBS pH 7.0	0.08–150	0.026	Serum	38
BDDE	—	0.1 mM NaCl	0.09–250	2.1	—	21
BDDE	—	BR pH 2.25	8–1000	7.7	Urine	This work

<sup>a</sup> Abbreviations: 3DGH – three dimensional graphene hydrogel, AuNPs – gold nanoparticles, BDDE – boron-doped diamond electrode, BR – Britton–Robinson buffer solution, CD – cyclodextrin, CPE – carbon paste electrode, CTAB – cetyltrimethylammonium bromide, Fc – ferrocene, FCNs – functionalized carbon nanospheres, GCE – glassy carbon electrode, GCPE – glassy carbon paste electrode, GF – graphene foam, GNS – graphene nanosheets, GO – graphene oxide, GPE – graphite paste electrode, IDA – interdigitated microelectrode array, ITO – indium tin oxide, LCR – linear concentration range, LOD – limit of detection, MWCNT – multi-wall carbon nanotubes, Nf – nanofibers, NPs – nanoparticles, PAA – polyaspartic acid, PBS – phosphate buffer solution, PDDA – poly(dimethyl diallyl ammonium chloride), PEDOT – poly(3,4-ethylenedioxythiophene), PGE – pencil graphite electrode, POMANS – polyortho-methoxyaniline nanostructures, PP – polypyrrole, rGO – reduced graphene oxide, and SPE – screen printed electrode.

UA stock solution (Fig. 6). For each sample, the found UA concentration together with the standard deviation (SD) value and the respective confidence interval ( $L_{1,2}$ ) for 95% probability is summarized in Table 4. The concentrations of UA were compared to reference values (1.4–4.4 mM) for human urine stated in the literature.<sup>7</sup> Based on these values it can be concluded that the U1 sample contained an increased amount of UA (but it was still below the upper limit).

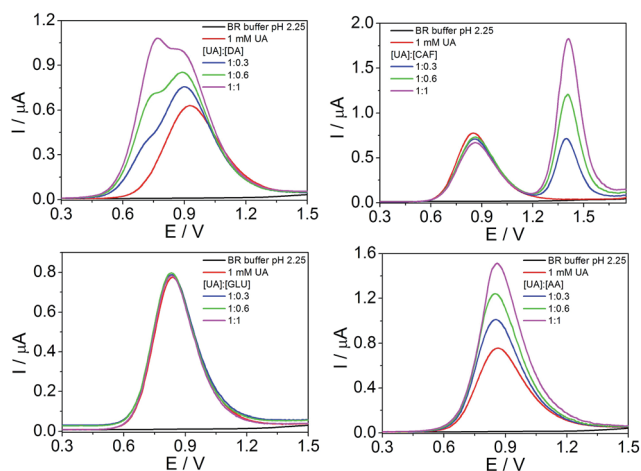


Fig. 5 DP voltammograms demonstrating the effect of the presence of dopamine, caffeine, glucose and ascorbic acid on the current response of 1 mM UA in BR buffer pH 2.25.

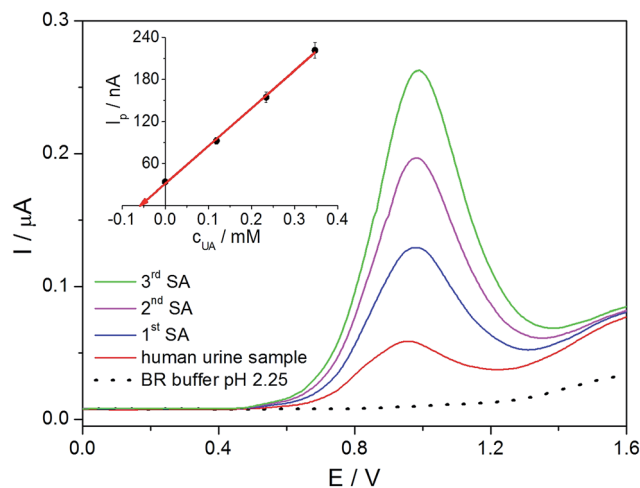


Fig. 6 DP voltammograms of urine sample (U2) analysis in BR buffer pH 2.25 using the 2000 ppm BDD electrode. Standard addition (SA) analysis is depicted in the inset.

Table 4 Analysis of urine samples using DPV ( $n = 3$ )

Sample	Found (mM)	SD (mM)	$L_{1,2}$ (mM)
U1	6.27	0.21	$6.27 \pm 0.35$
U2	2.84	0.07	$2.84 \pm 0.12$
U3	2.64	0.04	$2.64 \pm 0.07$

## 4. Conclusions

In this study, a set of boron-doped diamond electrodes with various B/C ratios (0–2000 ppm) has been used for the fast, simple and sensitive determination of UA. The sensitivities of particular methodologies have been compared and the detection limit of 7.7  $\mu\text{M}$  and good repeatability (relative standard deviation of 2.9% for  $n = 15$ ) were achieved using the 2000 ppm boron-doped diamond electrode. The current response of UA was also evaluated in the presence of common compounds found in urine. The developed electrochemical platform was applied to the determination of UA in human urine samples and the results were compared to the reference values stated in the literature. The impact of the presence of dopamine and ascorbic acid at their comparable concentration levels to UA may quite restrict the usefulness of this method in the direct analysis of biological samples with a complicated matrix.

## Conflicts of interest

There are no conflicts to declare.

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